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10/596,267	02/07/2007	Gaetano Giammona	1108.1003	4701

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LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER	
BROWE, DAVID	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
08/16/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/596,267	GIAMMONA ET AL.	
	Examiner	Art Unit	
	DAVID M. BROWE	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 5-19 are pending; claims 2-4 are cancelled.

Applicants timely submission of amendments and arguments in the reply filed July 26, 2010 in response to the First Action on a Request for Continued Examination is acknowledged.

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. Claim 16 is directed to a method for treating various diseases, but the method as written incorporates what in U.S. Patent practice are regarded as two distinctly different processes; the one directed to making a composition (i.e. "preparing") and the other to using a composition (i.e. "administering"). Thus, one of ordinary skill in the art would not be definitively apprised whether or not a method of making or a method of using the composition according to claim 8 is being claimed. This claim is an omnibus type claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 5-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromberg *et al.* (U.S. Patent Application Pub. No. 2003/0152623), in view of Blum *et al.* (U.S. Patent No. 6,294,591), Giammona *et al.* (*Biochimica et Biophysica Acta 1428(1999): 29-38*), and Cavazza (U.S. Patent No. 6,013,670).

Applicant Claims

Applicants claim an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), suitably derivatised with insertion of the photo-cross-linkable groups glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain, in the presence of acid comonomers. The acid comonomer is methacrylic acid or acrylic acid. The irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation. The matrix is preferably in the form of microparticles; and can also be in the form of nanoparticles, gels, films, cylinders, or sponges.

The matrix can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use. The excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers. The active ingredient(s) is selected from the group consisting of analgesic agents, antitussive agents, bronchodilators, antipsychotics, antihypertensive agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents, hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents,

cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride, cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof. The alkanoyl L-carnitine is selected from the group consisting of acetyl, propionyl, butyryl, valeryl, and isovaleryl L-carnitine.

Applicants further claim a method of treating a patient or an animal in need thereof with the matrix composition, administered by the parenteral or vaginal routes, for the treatment of cardiovascular, nervous system, intestinal and tumor diseases, wherein the intestinal disease is chronic ulcerative colitis or Crohn's disease, and the drug useful for the treatment of chronic intestinal disease is propionyl L-carnitine.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Bromberg *et al.* disclose an anionic hydrogel matrix obtained by cross-linking of polymers (Pg. 2, sec. 0012; Pg. 3, sec. 0013-0014; Pg. 4, sec. 0038; Pg. 5, secs. 0049-0052). The polymer is any polyaspartamide, which would encompass the specific polyaspartamide, α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) (Pg. 5, secs. 0050, 0052). The matrix is preferably in the form of microparticles (Pg. 25, sec. 0193)

The matrix can contain one or more active ingredients and pharmaceutically acceptable excipients; and is for oral use (Pg. 4, sec. 0039; Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171, 0180; Pg. 24, secs. 0182-0183). The excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers, and acrylic acid polymers (Pg. 23, sec. 0180). The active ingredient(s) is selected from the group consisting of analgesic agents, antitussive agents, bronchodilators, antipsychotics, antihypertensive

agents and coronary dilators, selective 6-2 antagonists, calcium antagonists, anti-Parkinson agents, hormones, non-steroidal and steroidal anti-inflammatory agents, antihistamines, spasmolytics, anxiolytics, antidiabetic agents, cathartics, anti-epileptic agents, anti-cancer agents, disinfectants, sodium fluoride, cardioactive agents, and L-carnitine and/or alkanoyl L-carnitine or a pharmaceutically acceptable salt thereof (Pg. 21, secs. 0137, 0144; Pg. 22, secs. 0145, 0147-0149, 0152-0154; Pg. 23, secs. 0171).

Bromberg *et al.* further disclose a method of treating a patient or an animal in need thereof with the matrix composition; administered by the parenteral or vaginal routes, for the treatment of cardiovascular, nervous system, intestinal and tumor diseases (Pg. 20, secs. 0134-0135; Pg. 21, secs. 0136, 0139-0142, 0144; Pg. 24, sec. 0184-0185).

Blum *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of acrylate or methacrylate copolymers, derivatised with photo-cross-linkable groups, in the presence of acid comonomers (Col. 1, lns. 6-7, 12-18, 53-56, 63-67; Col. 2, lns. 1-3, 30-34; Col. 3, lns. 66-67; Col. 4, lns. 1-10, 22-23, 50-51). The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain of the polymers; the acid comonomer is methacrylic acid or acrylic acid (Col. 3, lns. 66-67; Col. 4, lns. 1-10). The irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation (Col. 2, lns. 4-13).

Giammona *et al.* disclose an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA) polymers,

derivatised with photo-cross-linkable groups. The photo-cross-linkable groups are derived from the insertion of glycidyl methacrylate (GMA) in the side chain of the polymers; and the irradiation agent is selected from the group consisting of gamma rays, beta rays, and ultraviolet radiation.

Cavazza discloses the therapeutic use of alkanoyl L-carnitines and their pharmaceutically acceptable salts thereof in compositions for the treatment of ulcerative colitis (Col. 1, lns. 5-10, 54-56; Col. 2, lns. 2-9, 15-20). The alkanoyl L-carnitine is selected from the group consisting of acetyl, propionyl, butyryl, valeryl, and isovaleryl L-carnitine; the preferred alkanoyl L-carnitine is propionyl L-carnitine (Col. 2, lns. 2-9).

Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Bromberg *et al.*, while disclosing an anionic hydrogel matrix made by cross-linking polyaspartamide polymers, do not explicitly disclose that the specific polyaspartamide polymer is α,β poly(N-2-hydroxyethyl)D,L aspartamide (PHEA), derivatised by insertion of glycidyl methacrylate (GMA) or methacrylic anhydride (MA); and that the cross-linking of polymers is achieved by beta-, gamma-, or UV-irradiation in the presence of acid comonomers. Further, Bromberg *et al.*, while disclosing that the matrix can contain active agents and be administered for the treatment of disease, do not explicitly disclose that the specific active agent is propionyl L-carnitine; and that the matrix is administered specifically for the treatment of ulcerative colitis. These deficiencies are cured by the teachings of Blum *et al.*, Giammona *et al.*, and Cavazza.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Bromberg *et al.*, Blum *et al.*, Giammona *et al.*, and Cavazza, outlined *supra*, to devise applicants claimed invention. Cross-linked polymer matrix synthesis traditionally required the use of toxic initiators and contaminating chemical cross-linking agents, often used unwanted or unpleasant solvent systems, and required additional laborious purification steps (Blum *et al.*, Col. 1, lns. 18-52; Giammona *et al.*); an approach not optimal for preparing products intended for medical or veterinary use. A skilled artisan, therefore, would be motivated to synthesize a stimulus-responsive, cross-linked polyaspartamide hydrogel matrix, as taught by Bromberg *et al.*; with the clean, safe, and effective irradiation-mediated cross-linking approach via insertion of GMA and MA groups and use of acid comonomers, as taught by Blum *et al.*; using a particular polymer, such as PHEA, that is nontoxic, resistant to damage from radiation, and that has previously been shown to be cross-linkable by insertion of GMA, as taught by Giammona *et al.*; with the reasonable expectation that this approach will successfully produce a clean, safe and effective drug delivery vehicle for use in the medical and veterinary fields, with less effort and toxic contamination, as shown previously (Blum *et al.*; Giammona *et al.*).

Further, since Bromberg *et al.* disclose that an anionic hydrogel matrix obtained by cross-linking of polyaspartamide polymers can contain a therapeutic agent or a pharmaceutically acceptable salt thereof, and be administered to a patient for the treatment of intestinal diseases, and since Cavazza teaches that propionyl L-carnitine or

its pharmaceutically acceptable salt can be administered to a patient in a composition for the treatment of ulcerative colitis, one of ordinary skill in the art would be motivated to insert propionyl L-carnitine or its pharmaceutically acceptable salt into the cross-linked anionic hydrogel matrix of Bromberg *et al.* with the reasonable expectation that this composition would successfully treat ulcerative colitis when administered to a patient in need thereof.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments/remarks filed July 26, 2010 have been fully considered but they are not persuasive.

The Bromberg *et al.* disclosure provides that the following were already known in the art at the time of the present application: *i)* an anionic hydrogel matrix obtained by irradiation-mediated cross-linking of polyaspartamide and/or other suitable polymers, *ii)* anionic hydrogel matrices in the form of microparticles, and *iii)* an anionic hydrogel matrix incorporating active agents and excipients which are administered to a patient or

animal by oral, parenteral or vaginal routes for the treatment of intestinal and other types of diseases. It would have been obvious to one of ordinary skill in the art within the meaning of 35 U.S.C. §103, based on the disclosure of Bromberg *et al.* and further employing the combination of the respective teachings of Blum *et al.*, Giammona *et al.*, and Cavazza, already discussed in detail above, to formulate an anionic hydrogel matrix obtained by irradiation-mediated cross-linking specifically of *PHEA derivatized by GMA and MA with acid comonomers* as the particular, suitably derivatized polyaspartamide polymer, and incorporating *propionyl L-carnitine or its pharmaceutically acceptable salt* as the specific active agent, which are administered to a patient or animal by oral, parenteral or vaginal routes for the treatment of *ulcerative colitis* as the specific intestinal disease.

Applicants argue, however, that *Bromberg does not provide for PHEA polymers derivatised by insertion of GMA or MA in the presence of acid comonomers*. While the Examiner agrees that Bromberg *et al.* do not explicitly disclose an anionic hydrogel matrix comprising specifically PHEA polymers derivatised by insertion of GMA or MA in the presence of acid comonomers; the disclosure of Bromberg *et al.* , that anionic hydrogels can be made from irradiation-mediated cross-linking of polyaspartamide; together with the respective teachings of Giammona *et al.* (the particular polyaspartamide PHEA derivatized with GMA for irradiation-mediated crosslinking to produce anionic hydrogels) and Blum *et al.* (polymer derivitization with GMA as well as MA with acid comonomers for irradiation-mediated cross-linking) outlined *supra* render this limitation obvious within the meaning of 35 USC § 103.

Applicants argue that Blum *et al. does not add anything to the deficiencies of Bromberg….is completely silent with regard to PHEA….is not an analogous prior art....and is not a reference reasonably pertinent to applicants endeavor because logically it does not command itself to an inventor's attention.* Applicants further note that Blum *et al.* discloses *preparing radiation crosslinkable polymers suitable for coatings, paints, adhesives, etc.*.

The Examiner maintains, contrary to applicants assertions, that Blum *et al.* is not only a pertinent reference, it is a key reference the teachings of which disclose the very heart of applicants invention. This position is supported by the following points:

a) Blum *et al.* disclose a general process for preparing radiation cross-linkable polymers in a clean, safe, and effective manner for use in compositions; the very heart of applicants research work is concerned with producing safe and effective cross-linked polymer hydrogel matrices that can be used to deliver active pharmaceutical agents to patients and animals for medical/veterinary treatment of disease.

b) Blum *et al.* disclose a process of preparing (meth)acrylic acid/(meth)acrylate copolymers for irradiation-mediated cross-linking by insertion of GMA and MA groups in the side chains in the presence of acid comonomers; and further disclose using these polymers with suitable agents and excipients in compositions. Preparing polymers for irradiation-mediated cross-linking in this manner, and employing the thus cross-linked polymers in compositions with suitable agents and excipients corresponds with what applicants are claiming as their invention. The Blum *et al.* teachings are further pertinent to applicants endeavor for the following reasons: *i)* (meth)acrylic acid/(meth)acrylate

polymers and copolymers are routinely employed in the pharmaceutical and medical arts, particularly in drug delivery vehicles; *ii)* applicants provide for the inclusion of acrylic acid polymers in their composition (claim 10); and *iii)* applicants have previously disclosed a process for preparing PHEA for irradiation-induced cross-linking by the insertion of GMA groups into the side chains, and preparing an anionic hydrogel matrix by irradiation-mediated cross-linking of the modified PHEA polymers.

c) The Blum *et al.* Patent is assigned to BASF Coatings AG. Its no surprise, therefore, that Blum *et al.* would suggest the best mode for the use of their photo-crosslinkable (meth)acrylate copolymers would be in coatings, paints, and surface adhesives. However, Blum *et al.* further note that their invention is not limited to use in coatings, paints, and surface adhesives; that their invention can be employed in any envisaged application, and that "*the selection of monomers for combination is made in accordance with principles familiar to the skilled worker, such that they satisfy the requirements of the envisaged application*", and that "*these requirements may differ greatly*". A person of ordinary skill in the pharmaceutical arts would thus readily recognize and be able to take advantage of the relevant teachings the Blum *et al.* reference affords to the pharmaceutical arts.

Thus, while *Blum is completely silent with regard to PHEA*, Blum *et al.* adds immensely to the deficiencies of Bromberg *et al.* by disclosing the process for preparing irradiation-crosslinkable polymers by suitably derivatising the polymers by insertion of GMA and MA into the side chains in the presence of acid comonomers, and that these acid comonomers are selected from methacrylic acid and acrylic acid.

Giammona *et al.* disclose the process of preparing irradiation-crosslinkable PHEA by insertion of GMA into the side chain, and preparing irradiation cross-linked hydrogel matrices from said modified PHEA. Applicants assert, however, that *Giammona is completely silent with regard to acid comonomers and methacrylic anhydride (MA)*. The Examiner contends, however, that it was already established and disclosed at the time of the present application that PHEA can be photo-crosslinked by insertion of GMA into the side chain, and thus any person of ordinary skill in the art would find it obvious from the disclosure of Blum *et al.* that MA can be inserted as well, and, further, that the photo-crosslinking reaction can advantageously proceed in the presence of acid comonomers.

Applicants further assert that *Cavazza is irrelevant*, and *only provides for the treatment of chronic inflammatory bowel diseases with lower alkanoyl L-camitines*. The Examiner, however, cannot agree that Cavazza is irrelevant. Since applicants claim a method of treating bowel diseases by administering alkanoyl L-carnitines, its obvious from the disclosure of Cavazza that this aspect of applicants invention is already known and is not patentable.

Therefore, for the aforementioned reasons, the 35 U.S.C. § 103 rejection of claims 1 and 5-19 is hereby maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID M. BROWE whose telephone number is 571-270-1320. The examiner can normally be reached on Monday-Friday 7:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DAVID M. BROWE
Patent Examiner, Art Unit 1616

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616